REMARKS

I. Status of the Claims

With this response, new claim 53 is added and claims 2-14, 16-48 and 51-52 are canceled without prejudice or disclaimer. Upon entry of the proposed amendments, claims 1, 15, 49, 50 and 53 would be pending.

II. Restriction/Election Requirement

Applicants acknowledge that the Office has made final the restriction/election requirement. For the reasons stated below, the elected claim subject matter is believed to be patentable over the cited art. Therefore, applicants respectfully request the Office to extend the search and examination to the full scope of the pending claims and to consider all of the pending claims in their entirety.

II. Claim Objections

Applicants acknowledge with thanks the Office's withdrawal of the objections to claims 15-16 based on informalities.

III. Claim Rejections - 35 U.S.C. § 112, ¶ 2

Applicants acknowledge with thanks the Office's withdrawal of the rejection of claims 1, 15-16 and 43 based on indefiniteness.

IV. Claim Rejections - 35 U.S.C. § 112, ¶ 1 - Written Description

Applicants acknowledge with thanks the Office's withdrawal of the rejection of claim 1 based on written description.

V. Claim Rejections - 35 U.S.C. § 112, ¶ 1 - Enablement

Applicants acknowledge with thanks the Office's withdrawal of the rejection of claim 1 based on enablement.

VI. Claim Rejections - 35 U.S.C. § 102(b)

Applicants acknowledge with thanks the Office's withdrawal of the rejection of claims 1, 15-16 and 43 based on anticipation.

VII. Claim Rejections - 35 U.S.C. § 103(a)

Claims 1 and 15 stand rejected as being unpatentable over Fitzhugh *et al.*, "Qualitative Thin-Layer and High-Performance Liquid Chromatographic Analysis of 1-Substituted Diazen-1-ium-1,2-diolates on Aminopropyl-Bonded Silica Gel", *Analytical Biochemistry* 301, 97-102 (2002) in view of Patani *et al.*, "Bioisosterism: A Rational Approach in Drug Design", *Chem. Rev.* 96, 3147-3176 (1996) and Ismail, "Important fluorinated drugs in experimental and clinical use", *J. Fluor. Chem.* 118, 27-33 (2002). Applicants respectfully traverse this rejection for the reasons presented below and in the response of December 22, 2010.

The evidence and arguments of record fail to establish a *prima facie* case of obviousness. A "prima facie case depends on whether the prior art provided a suggestion or reason to choose a specific lead compound for modification, or to make the specific modification of the compound at issue." *Sanofi-Synthelabo v. Apotex*, 550 F.3d 1075 (Fed. Cir. 2008); *cert. petition filed*, 78 USLW 3065 (Jul 24, 2009), quoting *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350 (Fed. Cir. 2007); *see* also, *Procter & Gamble Co. v. Teva Pharmaceuticals USA Inc.*, 556 F.3d 989 (Fed. Cir. 2009); and *Eisai Co. v. Dr. Reddy's Laboratories, Ltd.*, 553 F.3d 1353, 1358 (Fed. Cir. 2008). Neither Fitzhugh *et al.*, Patani *et al.* nor Ismail teaches or suggests either the specific lead compound or the specific structural modifications that are necessary to make applicants' claimed compounds.

The Office cites *Procter & Gamble Co. v. Teva Pharmaceuticals USA Inc.*, *supra.*, and *Altana Pharma AG v. Teva Pharms. USA, Inc.*, 566 F.3d 999 (Fed. Cir. 2009) for the proposition that "it is not necessary to select a single compound as a 'lead compound' in order to support an obviousness rejection." Final Office action, page 5. However, both decisions state that "post-KSR, a prima facie case of obviousness for a chemical compound still, in general, begins with the reasoned identification of ***a lead compound***." *Procter & Gamble Co. v. Teva Pharmaceuticals USA Inc.*, *supra.*, and *Altana Pharma AG v. Teva Pharms. USA, Inc.*, *supra.*, quoting *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d at 1357 (emphasis added).

Case law aside, applicants' previous response in no way implies, as the Office suggests, "that there is a requirement for the selection of ***only*** compound 2" as the lead compound. Final Office action, page 5 (emphasis added). In fact, it was the Office that singled out Fitzhugh *et al.*'s compound 2 as the lead compound for modification: "It would have been obvious to one of ordinary skill in the art at the time of the instant invention to substitute the terminal methyl hydrogens of the ethyl moieties of compound 2 taught by Fitzhugh, with the fluorine atoms to give trifluoromethyl moieties." Final Office action, page 7, citing non-final Office action, page 16. By contrast, applicants' response states that "the cited art offers no suggestion or reason for an ordinarily skilled artisan to consider ***any of*** Fitzhugh *et al.*'s compounds, let alone compound 2, as a starting point for developing new NO donors." Response of December 22, 2010, page 12 (emphasis added).

As the Office points out, *Altana Pharma AG v. Teva Pharms. USA, Inc.*, *supra.*, indicates that obviousness of a chemical compound "may be shown by identifying some line of reasoning that would have led one of ordinary skill in the art to select and modify a prior art lead compound in a particular way to produce the claimed compound." Final Office action, page 6. In *Altana*, the Court found "ample evidence" that one of skill in the art would have considered "compound 12" a lead compound for further development efforts because: (1) the '518 patent asserted that its compounds, including compound 12, were improvements over the prior art; (2) the '518 patent disclosed that compound 12 was one of the more potent of the eighteen compounds provided; (3) Teva's expert witness testified that one of skill in the art would have

selected the eighteen compounds of the '518 patent from which to pursue further development efforts; and (4) Altana itself had selected compound 12 for further development efforts.

In contrast to *Altana*, the evidence of record fails to show that any of Fitzhugh *et al.*'s diazeniumdiolates is either potent, an improvement over the prior art, or even particularly effective as an NO donor or a therapeutic agent such as to warrant further development efforts. At the time of applicants' invention, numerous NO donors had been identified. In the absence of any reason to select Fitzhugh *et al.*'s diazeniumdiolates from the vast number of known NO donors, one of ordinary skill in the art would not have been motivated to use any of Fitzhugh *et al.*'s diazeniumdiolates as a lead compound for designing new NO donors or therapeutic agents.

Moreover, at the time of applicants' invention, one of ordinary skill in the art would have known that diazeniumdiolates derived from secondary amines were highly unstable with very short half-lives. For example, Hrabie *et al.*, *Chem. Rev.* 102, 1135-1154, 1147 (2002) (copy attached), reveals that Fitzhugh *et al.*'s compound 3 has a half-life (*i.e.*, release rate) of 3.0 seconds, while Cao *et al.*, *Brit. J. Pharm.* 137, 1155-1162, 1157 (2002) (copy attached), reveals that Fitzhugh *et al.*'s compound 2 (*i.e.*, DEA/NO) has a half life of 2 minutes. Thus, the state of the art at the time of applicants' invention teaches away from the use of Fitzhugh *et al.*'s diazeniumdiolates of secondary amines (*e.g.*, compound 1, 2, 3 or 4) as lead compounds.

Even assuming *arguendo* that the cited references could have suggested Fitzhugh *et al.*'s diazeniumdiolates as lead compounds, they fail to suggest the specific modifications that are needed to make applicants' claimed compounds. "[U]nder KSR, 'it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound.'" *Procter & Gamble Co. v. Teva Pharmaceuticals USA Inc.*, *supra*., quoting *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d at 1350.

The Office contends that Patani *et al.* "provides motivation to substitute F for H in an active compound" (Office action, page 6) and that Ismail "provides motivation to utilize trifluoromethyl groups in active compounds" (Office action, page 7). The Office argues that the

motivation to fluorinate Fitzhugh *et al.*'s compound 2 "would have been the expectation of increased lipophilicity enhancing absorption and/or improved translocation across membranes to a target location" (Office action, page 7). As discussed above, the instability of Fitzhugh *et al.*'s compound 2 was known in the art. In light of compound 2's instability, one of ordinary skill in the art would not have been motivated to improve compound 2's pharmacokinetic or pharmacodynamic properties, whether by fluorination or other means.

Even assuming *arguendo* that one of ordinary skill in the art would have been motivated to modify compound 2, the evidence and arguments of record fail to provide any reason to select fluorine replacement over all other available alternatives. At the time of applicants' invention, one of ordinary skill in the art had a multitude of options for modifying Fitzhugh *et al.*'s compound 2. Although bioisosteric replacement is just one of many approaches "used by the medicinal chemist for the rational modification of lead compounds" (Patani *et al.*, pages 3147), bioisosteric replacement itself encompasses a broad range of functional groups, including monovalent groups (e.g., fluorine, hydroxyl, amino, methyl, chloro, bromo, thiol), divalent groups (e.g., -O-, -S-, -CH_2-, -NH-), trivalent groups (e.g., -CH=), tetravalent groups (e.g., tert-butyl, trimethylsilyl, trimethylgermyl), ring equivalents (e.g., -NH-, -CH_2-, -S-, -Se-, -O-, -CH-, -N-), cyclic or non-cyclic non-classical replacements and non-classical replacements of functional groups (e.g., hydroxyl, carbonyl, carboxylate, amide, thiourea, halogen). Although extensive, Patani *et al.*'s list of bioisosteric replacements is by no means "exhaustive" (Patani *et al.*, first paragraph, page 3148). Moreover, many of the bioisosteric replacements have potential drawbacks. For example, fluoro substtitution can lead to "loss of potency" (Ismail, second paragraph, page 30), while trifluoromethyl substitution can decrease biological activity (Ismail, third paragraph, page 29) or cause adverse reactions (Ismail, fourth paragraph, page 29). In view of the various tools available for rational drug design and the potential disadvantages of bioisosteric replacement, particularly fluoro and trifluoromethyl substitution, it is unclear how an ordinarily skilled artisan would have singled out fluorine replacement as the sole means for modifying Fitzhugh *et al.*'s compounds.

The Office asserts that "sole means for modifying" is not the requirement of *Altana Pharma AG v. Teva Pharms. USA, Inc.*, *supra*. However, applicants are not implying that "sole means for modifying" is a legal requirement. Rather, applicants are simply pointing out that to change Fitzhugh et al.'s compounds into applicants' claimed compounds, one of ordinary skill in the art would have had to select fluorine replacement, to the exclusion of all other forms of modification, including all the other bioisosteric replacements identified by Patani *et al.*, "as the sole means for modifying" Fitzhugh *et al.*'s compounds. Neither Fitzhugh *et al.*, Patani *et al.* nor Ismail provides any suggestion or reason to either select any one of Fitzhugh *et al.*'s compounds as a lead compound, or to modify any one of Fitzhugh *et al.*'s compounds in the precise manner that would be necessary to produce applicants' claimed compounds.

Based on at least the foregoing reasons, applicants respectfully request withdrawal of this rejection.

Should the Examiner have any questions regarding this application, he is encouraged to contact applicants' undersigned representative at (703) 201-7197.

Respectfully submitted,

/Suet M. Chong/

Suet M. Chong (Reg. No. 38,104)

Date: July 26, 2011

CORRESPONDENCE ADDRESS:

ARNOLD & PORTER LLP
Attn: IP Docketing
555 Twelfth Street, N.W.
Washington, DC 20004
(202) 942-5000 (telephone)
(202) 942-5999 (facsimile)